ON THE PHYSIOLOGICAL PROPERTIES OF THE GONADS AS CONTROLLERS OF SOMATIC AND PSYCHICAL CHARACTERISTICS: V. THE EFFECTS OF GONADECTOMY IN THE GUINEA PIG, ON GROWTH, BONE LENGTHS, AND WEIGHT OF ORGANS OF INTERNAL SECRETION.

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To be able to interpret correctly the changes in weight of an animal incident to experimental modification of the sex-gland conditions, such as total castration or spaying followed by sex-gland transplantations, it is necessary to know the relationship of the weight of the normal to the totally castrated and totally spayed animal. Certain investigators have employed relative weights of the rat and guinea pig as indications of modification of the sexual conditions (see Steinach and Holznecht), and certainly the reactions of the guinea pig, in this respect, are not sufficiently understood to justify such conclusions as have been announced.

Steinach takes for granted that, inasmuch as the male of both rats and guinea pigs is usually heavier than the female, the testis is responsible for an internal secretion liberated by the interstitial cells that promotes growth and otherwise leads to the production of maleness, whereas the ovary is responsible for a secretion that acts to retard growth. Acting upon this assumption, he utilizes the weight of an animal at practically any age to compare with a brother or sister animal to show the differential effects of sex-gland grafts.

In 1919 the writer called attention to the work of Stotsenburg ('09, '13) on the rat wherein the growth curve was shown to be independent of the testis, but the growth curve of females was reduced by the presence of the ovary—*i.e.*, totally spayed female growth curves were from 17 per cent. to 30 per cent. higher than that of their normal sisters. It is to be understood, therefore, for the rat, that relative weight increase in a spayed female bearing a

testis graft is due to the removal of the retarding influence of the ovary and not to an influence of the testis graft as claimed by Steinach. Sufficient data were presented in the second paper of this series[1] to show that Steinach's femininized and masculinized rats can not be so adjudged on the basis of differences in weight.

Since Steinach has applied the same principles to the guinea pig to detect changes in its sexual condition after operative procedures, the writer in 1921 criticized again such indiscriminate uses of weight records and mentioned an experiment under way to determine the fundamental reactions in weight upon removal of the gonads. The present paper embodies the results obtained from this investigation.

The growth of a series of guinea pigs, consisting of normal males and females, as well as totally castrated males and totally spayed females, was followed from birth to maturity (for one year). And in addition to determining the growth curves for the four classes of animals it appeared not only desirable to examine the glands of internal secretion for possible changes correlated with sex glands, but to examine as well the effect of castration and spaying on the growth of the long bones of the leg.

II. Material and Methods.

The animals for this experiment were selected from young born from our own laboratory stock at a time when the stock was able to supply a quantity within a relatively short period of time. Comparisons in weight were then made at approximately the same time of the year, as all the animals of this experiment were born between April 20 and August 27, 1920. The forty-six animals with which the experiment was begun were grouped in the following manner: 12 normal males, 11 castrated males, 12 normal females, and 11 spayed females. These were so caged as to be recognizable at any moment, and in such a manner that pregnancy was eliminated in the normal females in all but two cases.[2]

The animals were kept in the same room, in ordinary wire cages

[1] Moore, '19.

[2] Minot, 1891, has shown that pregnancy does not cause a permanent change in the weight of a female animal; a correction for the weight of the unborn young was made in these two cases of pregnancy.

16 x 16 x 30 inches, were fed daily with carrots and hay, and usually all cages were supplied with grain (corn, oats) twice each week. Each animal was weighed on each thirtieth day from birth to the end of one year (360 days). As each weighing was made by the writer, an absence of three weeks caused one weighing of some animals to be omitted.

To avoid differences due to the operation castration was accomplished by opening the peritoneal cavity of the young male by a mid-ventral incision; the spermatic cord was tied off considerably above the testis, and by cutting the cord below the ligature the testis was removed intact. Spaying was accomplished by means of two dorsolateral lumbar incisions (one on either side) tieing, or clamping for a short time, the ovarian blood vessels, and removal of the ovary with or without a considerable amount of the oviduct. Post-mortem examination showed that in every case the entire ovary had been removed. Each animal was castrated or spayed before the thirtieth day and in the majority it was done before the age of fifteen days.

As the experiment approached its termination each animal was killed with chloroform immediately after weighing (on the 360th day) and the following data recorded: total body weight (before killing), total body length, weight of the two thyroids, hypophysis (pituitary body), the two adrenals, spleen, sex glands where present, and the lengths of the femur, tibia, and fibula.

In weighing the glands, except the hypophysis, all were rapidly removed from the animal, cleaned of superfluous connective tissue, and placed together in a ground-glass covered container, weights being obtained by difference as each gland was removed to fixation bottles. The weights were obtained as rapidly as possible, hence the glands contained whatever blood or other fluids they possessed at the moment of removal.

In handling the pituitary, the cranial cavity was rapidly opened, cranial nerves severed as the brain was lifted off the floor of the cranial cavity, and the gland very carefully dissected from under the membranes and immediately dropped into a weighing tube containing the desired fixing fluids; the weight of the container and fluid had been determined immediately before the animal was killed. In all cases the hypophysis was in the killing fluid and

weighed within thirty minutes after the administration of chloroform. In each animal thyroids, adrenals, and hypophysis were preserved in Bouin's fluid or formol-Zenker's solution for subsequent histological study.

In bone measurement the two legs of each animal were stripped of muscle and boiled in a weak alkali solution for a short time, after which they were cleaned of all muscle and ligaments. They were then measured by means of graduated calipers (grad. to .01 cm.) and the length of the two corresponding bones averaged. Second measurements were made at a later date by Mr. N. F. Fisher, who was unacquainted with my measurements, and the two sets compared; in case of differences a third measurement was taken.

III. Growth Curves.

The weights of each animal of the experiment on each thirty days is given in Table I., and the growth curves for the four groups are shown in Fig. 1. These curves were constructed from an average of the weights of all animals in each of the four groups for each weighing period—*i.e.*, 30, 60, 90 days, etc.

Table I.

Showing Individual Weights of Each Animal up to 360 Days and the Averages for Each Group as a Whole at Each Weighing Period.

Animal.	30 da.	60 da.	90 da.	120 da.	150 da.	180 da.	210 da.	240 da.	270 da.	300 da.	330 da.	360 da.
						Normal Males						
X1.....	172	325	500	—	680	700	760	810	865	870	930	980
X2.....	205	305	440	640	—	740	770	825	830	885	895	835
X3.....	180	330	495	—	630	670	720	765	815	855	807	870
X4.....	162	270	450	625	—	730	805	855	930	980	980	967
X5.....	120	200	330	—	440	475	520	520	580	600	450	575
X6.....	210	375	580	—	680	715	770	810	825	890	970	950
X7.....	255	405	505	580	520	650	705	725	790	810	775	810
X8.....	340	540	—	725	830	930	980	1,065	920	1,040	1,115	1,120
X9.....	245	455	—	630	700	755	720	665	670	685	660	650
X10.....	155	295	—	425	490	500	535	555	585	605	650	550
X16.....	280	—	465	540	595	620	660	725	725	785	860	885
X22.....	—	510	560	670	810	920	1,040	1,080	1,150	1,220	1,195	1,280
Average..	211	364	480	604	637	700	749	783	807	852	857	872

Castrated Males

X11.....	135	245	—	365	410	490	510	540	565	600	600	555
X12.....	—	450	—	560	615	650	750	dead	—	—	—	—
X13.....	—	445	—	545	585	575	605	700	755	795	810	850
X14.....	165	285	400	465	535	615	690	735	800	835	870	940
X15.....	370	515	605	635	700	740	765	825	855	dead	—	—
X17.....	280	—	470	525	595	635	650	720	748	dead	—	—
X18.....	240	—	410	440	510	565	640	685	715	750	795	830
X19.....	270	—	450	500	580	640	725	770	dead	—	—	—
X20.....	—	365	415	415	510	555	530	585	580	620	655	695
X21.....	—	360	455	545	570	650	dead	—	—	—	—	—
X23.....	—	415	470	605	735	740	845	907	925	940	1,015	995
Average..	243	385	459	509	576	623	671	718	742	756	791	810

Animal.	30 da.	60 da.	90 da.	120 da.	150 da.	180 da.	210 da.	240 da.	270 da.	300 da.	330 da.	360 da.

Normal Females

Y1.....	175	305	460	—	640	670	740	700	700	700	730	807
Y2.....	285	370	510	645	—	760	800	875	900	945	980	880
Y3.....	197	265	475	620	—	770	780	815	855	865	855	925
Y4.....	170	210	390	515	—	640	675	750	770	805	875	875
Y5.....	130	245	360	—	590	dead	—	—	—	—	—	—
Y7.....	180	390	615	—	670	720	760	dead	—	—	—	—
Y8.....	222	380	—	590	640	665	740	785	790	815	870	900
Y9.....	215	360	—	550	590	645	705	590	670	760	815	800
Y10.....	250	390	—	580	620	685	720	780	835	850	830	890
Y19.....	—	390	435	520	625	640	685	745	795	855	900	975
Y20.....	—	335	370	435	510	540	585	620	655	700	730	785
Average..	202	330	452	557	610	673	719	740	774	810	843	871

Spayed Females

Y11.....	240	390	—	605	660	735	780	840	870	905	dead	—
Y12.....	370	530	—	680	735	740	745	760	835	917	930	995
Y14.....	163	280	375	455	515	593	645	700	765	815	850	915
Y15.....	300	400	485	550	590	580	645	720	700	740	715	700
Y16.....	262	—	440	490	565	620	630	655	680	740	810	850
Y17.....	—	330	365	435	510	560	575	625	650	695	755	800
Y18.....	—	345	390	460	520	570	595	630	655	695	755	800
Y21.....	—	395	510	590	630	695	dead	—	—	—	—	—
Y22.....	—	415	470	575	680	735	795	845	835	890	920	925
Y23.....	—	470	490	520	625	700	690	803	850	935	1,020	1,045
Average..	267	395	440	536	603	652	677	730	760	815	844	879

Examining the growth curves one sees that each group as a whole ascends in an unbroken curve from the first weighing to the last one made on the 360th day. A few animals of each series showed individual temporary loss in weight, but as a group the increases from month to month were continuous.

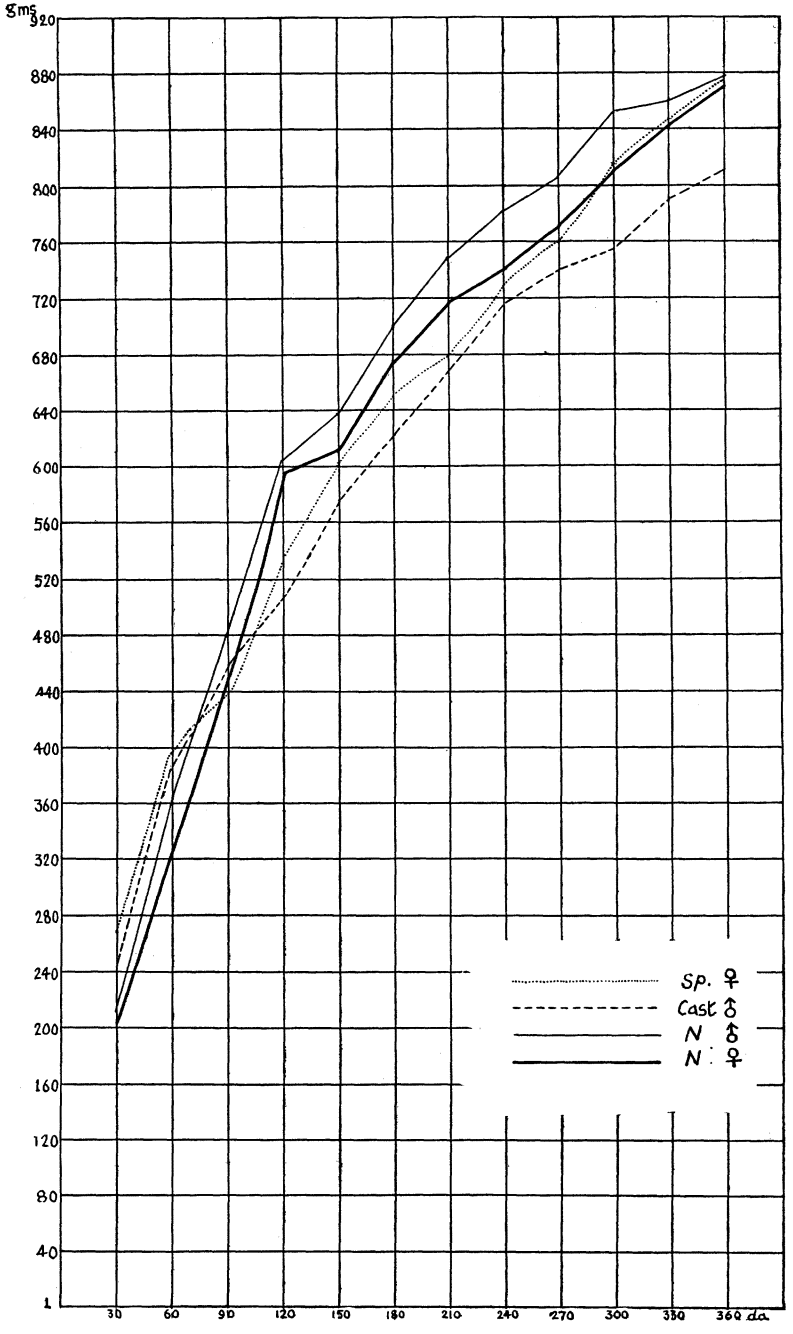

FIG. 1. Growth curves for normal males (*N*♂), normal females (*N*♀), totally castrated males (*Cast* ♂), and totally spayed female (*Sp* ♀), guinea pigs for one year from birth. The curves were constructed from the average weight of each group, on 30, 60, 90 days, etc., as given in Table I.

In reference to growth curves, as well as to all other elements of the investigation, three particular points have been kept in mind: (1) the possible demonstration of sexual differences, (2) the effects conditioned by total castration, and (3) the effects conditioned by total spaying.

Sexual Differences.—Comparing the growth curves of the normal animals, male with female (Fig. 1), one sees that the males are constantly the heavier up to the end of the first year of growth, when the average weight of the two groups is the same. This agrees with the findings of Minot ('91), who demonstrated that the male guinea pigs were heavier than the females (as a group) up to about the end of the first year, after which the female growth curve crossed that of the males, and from this time on the females were from 1 per cent. to 7 per cent. heavier than the males.

Total Castration.—From a glance at the growth curves in Fig. 1, or reference to the average weights from both groups of animals as seen in Table I., it becomes apparent that castrated males are lighter in weight than normal males at all ages from ninety days to the end of one year. In other words, castration causes a relative loss in weight in the guinea pig when compared with the normal male.

Total Spaying.—Spayed females also exhibit a relative loss in weight when compared with the normal females. The young spayed females at the beginning of the experiment were slightly heavier than the normal females, due merely to chance variation in weight in the selection of the animals, but at the age of ninety days the normal females are slightly heavier and continue so throughout the experiment until the 360th day, when the spayed females averaged approximately 1 per cent. heavier than the normal females. One is forced to conclude from this data that spaying results, for a certain period, in a decreased body weight (compared with the normal females), but that this loss is made good at a later time.

Discussion.—The particular point in mind for solution was whether the weight of an animal could be depended upon to offer an index of its sexual condition in case of sex-gland transplantations. As mentioned above, Steinach has placed considerable emphasis on the differences in weight after castration and spaying

and subsequent transplantations of sex glands of the opposite nature. To mention specific data, Steinach and Holzknecht ('16, pp. 493 and 495) publish the following weights: (*a*) normal male, 980 grams; normal female, 808 grams; femininized males, 516 grams; and (*b*) normal female, 845 grams; normal male, 1,002 grams; masculinized female, 1,200 grams. Since the above writers believe that an ovary graft femininizes an animal, the data of (*a*) theoretically shows that the ovary graft has so functioned as to reduce the weight of the male to such an extent that it is 47 per cent. lower in weight than had it continued a normal male, and is indeed 36 per cent. below the weight of a normal female; thus the ovarian grafted male is more female than the normal female herself. Also, since a testis graft masculinizes an animal, the data of (*b*) indicates to them that the female, as a result of the testis graft, has gained 42 per cent. in weight above what it would have been had it remained a normal female, and to have increased in weight 19 per cent. above the normal male; thus, here also, the animal is considered much more a male, as an after effect of the testis graft, than the normal male.

Instead of showing that the ovary has a decided effect in lowering body weight, my own results on the guinea pig show that females deprived of the ovaries are lighter in weight up to the end of the first year than those possessing ovaries. While it is true the normal males are heavier than castrated males (indicating, possibly, that the testis promotes growth), nevertheless the averages of the two groups throughout the year give a difference of but 7.6 per cent. in favor of the normal males, as against the tremendous differences in the case of Steinach and Holzknecht. Comparisons of animals of the same litter do not afford more convincing arguments in favor of weight comparisons. One example being sufficient, attention is directed in Table I. to females Y19 and Y20. These two animals of the same litter (sisters) were kept in the same cage throughout their entire life and hence possessed equal chances of growth; each suffered no reversals, but continued to increase consistently for the 360 days, yet Y19 maintained a weight from 15 to 20 per cent. above Y20 throughout the entire period of observation. Let us suppose that Y19 had been spayed and received a testis graft at an early age. Comparisons

would have shown that the animal had increased 20 per cent. in weight, as a result of the experiment, even had the testis not grown.

Without further discussion of the above point, it should be clearly demonstrated to the reader that such a comparison of weights of two or three animals, chosen at random, is absolutely unreliable as evidence of their sexual nature. As the writer has pointed out previously, the same criticism applies to rats. Since the fallacy of such comparisons can not but be realized, it follows that as evidence of masculinization and femininization such data should be ruled out when considering the value of the various types of data presented to support this idea.

Turning to the literature for actual data supporting the well-established idea that castration or spaying causes an overgrowth in body weight in animals (particularly the former), one realizes that there are indeed few experiments adequately controlled that give results supporting this idea.

Stotsenburg is apparently the first to carry out experiments on mammals determining the effects of gonadectomy wherein a sufficient number of animals were utilized to warrant definite conclusions. Reference was made above to these results. He found that the growth curves of normal and castrated male rats were very similar, and that castration in the rat did not result in a relative increase in weight from birth to maturity. In spayed females, however, there was a decided relative increase in weight as compared with normal females; the increase amounted to from 17 per cent. to 30 per cent. above the normal.

Hatai ('13, '15) confirms in general the above conclusions of Stotsenburg, though in a late paper he is inclined to believe that castration of male rats causes a slight relative increase in body weight over the control males; this, however, is not more than 3 per cent. to 5 per cent. And in spayed females there is both an increase in relative body weight and body length.

Livingston ('16) studied the effect of castration and spaying in the rabbit, but it is difficult to properly interpret his data, since the relative ages of his animals were unknown. Furthermore, he states that at the time of operation the ages varied from a few weeks to about one year, and that body weights ranged from 300

grams to more than two kilos, yet averages were taken on the group as a whole. In his Fig. 7 (curves 13 and 14), however, in which normal males controlled operated males and normal females the operated females from the same litter (ages not given), the indications are that the castrated males increase in weight, compared with the normal males, for a period of four months after operation. One is unable to judge, however, the comparative ages of all concerned and undoubtedly this would make a considerable difference in the results. This writer, as well as Hatai, believes that after castration there may or may not be a hypertrophy of the hypophysis, depending upon unknown factors; if hypertrophy does not take place, the animal undergoes a relative increase in weight, whereas there is an absence of a relative body weight increase if the hypophysis does not so react. If this is later proven to be correct, one will be unable to properly interpret weight differences following sex-gland removal without considering the possibilities of secondary influences dependent upon the hypophysis. One is led to believe from the experiments of Livingston with the rabbit that totally spayed females are hindered in growth; his curves show the normal female weight to be above that of the spayed females.

Thus Stotsenburg and Hatai are in practical agreement that the testis does not influence the growth of the rat, whereas in the rabbit Livingston believes that the testis retards growth; castrated animals are heavier than controls. My own experiments show but little effect in the guinea pig from castration, though there is a slight indication that the testis stimulates growth. As to the effects of the ovary on growth, Stotsenburg and Hatai agree that elimination of the rat ovary results in relative increases in the growth curves; Livingston, however, believes that ovariotomy lowers the growth curves in the rabbit. In the guinea pig my experiments show a slightly reduced growth curve for the spayed females up to the end of the first year.

IV. Body Length of Normal and Operated Animals.

The total body length of each animal was determined as each was killed on the 360th day, and it appeared desirable to record these observations for the bearing they may have on growth in

general. The body length of each animal is given in Table II., as well as the average lengths for the different groups as a whole. From the average of each group one sees that the groups have essentially the same relationship to each other as the average weight determinations—*i.e.*, in the order, normal males > normal females > spayed females > castrated males. This indicates that the weight as a whole is due to a general growth rather than in certain groups to excess fat deposition as a secondary result from some specific action of the glands of internal secretion.

V. Weight of the Hypophysis.

According to many investigators there is a more or less specific effect upon the hypophysis from gonadectomy; however, many of the conclusions found in the literature are diametrically opposed. It appears that too often merely gross weight comparisons of this small gland from two animals are used rather than a comparison of percentages of body weight; where small numbers of animals are used the latter method would offer more adequate means of studying specific reactions of the gland.

Table II.

Showing Individual Weights of Organs of Internal Secretion and Lengths of Bones and the Averages for the Same for the Various Groups.

Animal No.	Body Wt., Grams.	L'gth. Cm.	Hypophysis, Grams.	Thyroids, Grams.	Adrenal, Grams.	Spleen, Grams.	Femur, Cm.	Tibia, Cm.	Fibula, Cm.	Sex. Gl., Grams.
				Normal Males						
X1.....	980	31.6	.0116	.1646	.7300	1.0084	4.64	5.01	4.16	4.4406
X2.....	835	30.0	.0192	.2116	.8118	1.0225	4.62	5.08	4.30	3.9619
X3.....	870	30.4	.0152	.1642	1.1260	.6178	4.57	4.855	4.15	3.7612
X4.....	967	32.9	.0192	.1710	.7419	.6899	4.77	5.135	4.35	5.3212
X5.....	575	29.5	.0136	.1088	.5208	.7012	4.525	4.80	4.045	2.0410
X6.....	950	30.9	.0072	.1421	.9566	1.1141	4.51	4.95	4.100	5.9152
X7.....	810	27.5	.0144	.1402	.8900	.9570	4.46	4.87	4.16	4.6440
X8.....	1,120	32.0	.0150	.1886	1.3630	.9094	4.715	5.13	4.28	6.5590
X9.....	650	29.7	.0116	.1270	.6872	.5485	4.465	4.86	——	2.8073
X10....	550	27.0	.0104	.1330	.7433	2.9542	4.37	4.70	3.67	2.4573
X16....	885	30.6	.0147	.1306	.6580	.7095	4.645	5.00	4.24	4.2510
X22....	1,280	33.0	.0170	.1400	.7152	1.1344	5.095	5.61	4.70	5.0086
Average.	872	30.4	.0140	.1518	.8286	1.0305	4.615	5.00	4.196	4.2640

Castrated Males

X11....	555	28.0	.0018	.1546	.5200	.4034	4.4	4.765	——	
X13....	850	29.0	.0121	.1829	.7595	.8134	4.495	4.855	4.10	
X14....	940	28.5	.0154	.1826	.7100	1.6100	4.40	4.85	4.135	
X18....	830	29.0	.0130	.1208	.8598	.7920	4.45	4.95	4.205	
X20....	695	28.0	.0141	.1786	.7154	.8522	4.475	4.875	4.140	
X23....	995	29.5	.0170	.1700	.9584	.9516	4.780	5.185	4.380	
Average.	810	28.6	.0122	.1649	.7538	.9037	4.5	4.915	4.192	

Animal No.	Body Wt., Grams.	L'gth. Cm.	Hypophysis, Grams.	Thyroids, Grams.	Adrenal, Grams.	Spleen, Grams.	Femur, Cm.	Tibia, Cm.	Fibula, Cm.	Sex. Gl., Grams.

Normal Females

Y1.....	807	29.7	.0165	.2180	.7054	1.3174	4.37	4.70	3.93	.1302
Y2.....	880	30.1	.0035	.1610	.7793	.7526	4.47	4.92	4.195	.1918
Y3.....	925	29.2	.0142	.1372	1.0010	1.3911	4.375	4.725	4.015	.1766
Y4.....	875	29.1	.0164	.1710	.5230	1.3171	4.31	4.68	4.01	.1434
Y8.....	900	30.6	.0124	.1246	.6050	.7596	4.49	4.95	4.21	.1294
Y9.....	800	29.5	.0174	.1165	.7721	1.0550	4.47	4.945	4.265	.1784
Y10....	890	29.3	.0162	.1204	.5314	.9710	4.455	4.78	4.06	.1050
Y19....	975	29.0	.0170	.1873	.7169	.9610	4.57	4.95	4.22	.2158
Y20....	785	29.0	.0166	.1742	.5708	1.3666	4.575	4.865	4.125	.1552
Average.	871	29.5	.0150	.1567	.6894	1.0990	4.454	4.835	4.114	.1584

Spayed Females

Y12....	995	29.5	.0144	.2146	.6645	1.2505	4.61	5.14	4.345	
Y14....	915	29.0	.0134	.2096	.6407	1.1181	4.30	4.8	4.100	
Y15....	700	29.2	.0142	.1650	.5416	1.1551	4.595	5.15	4.300	
Y16....	850	29.2	.0164	.1718	.5418	.8070	4.68	5.06	4.350	
Y17....	800	27.0	.0128	.1412	.5286	.8470	4.50	4.91	4.220	
Y18....	800	28.5	.0119	.1534	.3540	.9126	4.55	4.95	4.240	
Y22....	925	29.0	.0118	.1498	.5760	.8744	4.56	5.05	4.300	
Y23....	1.045	29.5	.0124	.1348	.6456	.7556	4.70	5.07	4.345	
Average.	879	28.8	.0134	.1675	.5616	.9625	4.562	5.01	4.275	

In my own experiment the average gross weights of several glands from animals of the same age, sex, and operated condition form the basis of the comparison, the average body weights of the same lots of animals being known. Table II. gives the weight of individual hypophyses as they were removed from the animal on the 360th day of life. The weights of all the hypophyses for each group were averaged and a comparison of these average weights should give as good an indication of the reactions, if any, as any method of comparison that could be used.

Sexual Differences.—Comparing the average weight of the twelve normal male hypophyses (.0140 gram) with the average of nine normal female glands (.0150 gram), we see that the female hypophysis is 7.1 per cent. heavier than that of the male. And comparing the average body weights of the same two groups, one sees a difference of but one gram; in other words, the average body weights of the two groups are almost identical. There appears, therefore, to be a slight sexual difference in the weight of the male and female guinea pig hypophysis at the end of one year's growth, the female hypophysis being slightly heavier than the male.

Castration.—Comparing the average weights of the twelve normal male hypophyses (.0140 gram) with the average of the six castrated male hypophyses (.0122 gram), we find that the normal male hypophysis is 14 per cent. heavier than the hypophysis of castrated males. Comparing the body weights of these two groups, the normal males are 7.6 per cent. heavier than the castrated males, or, in other words, the relationship of the hypophysis of the normal male to that of the castrated male is proportionally greater than the relationship of the body weights. Thus we conclude that castration causes a relative decrease in the hypophysis as well as an actual one, as shown by the figures in the table.

Spaying.—If one compares the average weight of the hypophyses of the nine normal females (.0150 gram) with the average weight of the same gland of the eight totally spayed females (.0134 gram), it will be seen that the normal female hypophysis is 12 per cent. heavier than the hypophysis of the spayed females. And looking at the ratio of body weights of the two groups, it will be seen that the spayed females are approximately 1 per cent. heavier than the normal females. Thus at the end of one year the normal female hypophysis is both relatively and actually heavier than that of the spayed females, or, in other words, total spaying causes a decrease in weight of the hypophysis.

Discussion.—It has been impossible to find in the literature more than one or two observations wherein the weight relations between the hypophysis of the normal male and female of any group of animals have been determined. It would appear that a knowledge of sexual differences would be of great value in attempting to

unravel the existing relations between the sex glands and the hypophysis. Hatai ('13) has shown that the hypophysis of the female albino rat is more than twice the weight of that of the male, and that in the Norway rat weight difference is also constant, but of less degree than in the albino variety. As noted above, the female guinea-pig hypophysis was heavier than the male gland, though the difference in this case is but 7 per cent. Too few determinations have been made, however, to warrant the conclusion that the same result, in general, would hold for other animals.

There is a great amount of controversial evidence on the effects of gonadectomy on the hypophysis, not only among the different groups of animals investigated, but also for the same group investigated by different workers. Fischera ('05) maintained that the hypophysis increased very materially in weight when gonadectomy was performed on the common fowl, cattle, rabbit, guinea pig, and buffalo. Marrassini and Luciani ('11), however, denied an increase in the hypophysis under these conditions for practically the same group of animals utilized by Fischera. And since the publications of the latter an increase in the hypophysis following gonadectomy has been reported for the female dog and rabbit (Parhorn and Goldstein, '05), male dog and rabbit (Cimorini, '08), male and female rat (Hatai, '13); but an increase of the hypophysis has been denied for the male guinea pig (Pirsche, '02), the male of the common fowl, cattle, dog, rabbit, guinea pig, sheep, and the female guinea pig (Marrassini and Luciani, '11). These very different results are undoubtedly due to inadequate controls. It is very difficult to judge, in most instances, if the conclusions drawn are warranted by the materials considered; even if they are, the majority of observations have been made upon an inadequate number of animals, many times even upon animals of a different stock. It appears that the observations of Hatai stand almost alone in respect to the materials used, for in this investigation the growth relations are sufficiently understood and conducted upon a sufficient number of animals to warrant an adequate comparison.

Without attempting to discuss the ideas of the various writers, advanced as explanations of their own particular results, I will

but mention a correlation between the sex glands and the hypophysis first mentioned by Hatai and approved by Livingston. Hatai called attention to an apparent reciprocal relationship between these two glands, of such a nature that different effects can be noted in subsequent growth. He noted that castrated animals showing an hypophyseal hypertrophy did not show an overgrowth in body weight, and conversely if the hypophysis had not increased in weight, relative to the normal, the animal did show an overgrowth in body weight. "Thus if a compensatory growth of the hypophysis does not follow, as is the case after spaying, the product of the unaltered gland must be employed for two purposes: one, to replace the ovarian hormone, and, two, for the normal uses, whatever they may be."

Later experiments led Hatai to believe that his assumptions were correct, as further observations substantiated the idea. Livingston ('16) agrees with the assumption of Hatai inasmuch as the results of his series of gonadectomized rabbits could be interpreted on this basis. He states that when the body responds by an increase in weight, even though slight, the pituitary does not show a compensatory hypertrophy.

My own observations on the guinea pig, however, do not accord with the idea that in the absence of hypophyseal hypertrophy an overgrowth of body proportions follow. The average weight of the normal male hypophysis was 14 per cent. greater than that of the castrated male, whereas the average body weight of the castrated males was less than that of the normal animals; and similarly the average weight of the normal female hypophysis was 12 per cent. greater than that of the spayed females; and, again, the average total body weight of the spayed female was below, or almost identical with, that of the normal female. And in each of the above cases, to substantiate the hypothesis, there should have been a relative increase in the body weight of the gonadectomized animals, since the hypophyseal weight was less. It remains, therefore, for subsequent investigation to prove that there is this general relationship that has been indicated by the rat and rabbit material.

VI. Growth of Thyroids.

The actual weights of the thyroid glands of each animal of the series are shown in Table II. and the average weight of the glands of each group as well (both thyroids weighed in each case).

Sexual Differences.—When the average weights of the twelve normal male thyroids (.1518 gram) are compared with the average weights of the nine normal female glands (.1567 gram), we see that the normal female thyroids are approximately 3.2 per cent. heavier than those of the normal males. Since the total body weights of the two groups do not vary more than one gram, it appears that the female guinea-pig thyroids are heavier than the male glands.

Castration.—Comparing the average thyroid weights of the normal males (.1518 gram) with those of the castrated males (.1649 grams), the thyroids of the castrated males appear to be 8.6 per cent. heavier than those of the normal animals. But since the body weight of the normal males is 7.6 per cent. greater than that of the castrated males, the relative differences of thyroid weights are really considerably greater than the differences of their actual weights. Hence we may conclude that castration in the guinea pig favors the growth of the thyroids.

Spaying.—The average weight of the normal female thyroid (.1567 gram) compared with the average of the spayed females (.1675 gram) reveals a difference of 6.8 per cent. in favor of the spayed animals. Since the averages of body weight favor the spayed females by only 1 per cent., we see that elimination of the ovaries favors growth of the thyroids in the females.

To the writer's knowledge there is no authenticated observation of a sexual difference in the weight of the thyroid gland in any animal. It must be emphasized that results obtained from a comparison of one or two animals are decidedly unreliable and of little value.

In all cases where a sufficient number of animals of corresponding ages have been compared the variability in weight is such that results of a definite character are not indicated. Thus Livingston ('16) determined the weights of the thyroid glands in a large number of rabbits, normal and operated, but the degree of weight

variability was so pronounced that no definite conclusions were warranted. Hatai ('18) definitely states that there is no apparent sexual difference in the weight of the thyroids in the rat. Furthermore, the variability in thyroid weight was so pronounced among the operated rats that results of a definite character were not indicated.

In the guinea pig comparison of the average weights of male and female thyroids at the end of one year favored the females to a slight extent.

Gonadectomy apparently favors the growth of the thyroid in the guinea pig inasmuch as each operated group showed a definite increase in the thyroids at the end of one year. However, in view of the many failures to establish a definite effect, one must be very skeptical indeed in applying these results as a general effect of gonadectomy. Obviously repetition of the experiment is necessary before general principles can be held as established even for the guinea pig.

VII. Growth of Adrenals.

The individual weights of the adrenals (two in each case) can be seen by reference to the different groups given in Table II.

Sexual Differences.—When one compares the average weight of the normal male adrenals (.8286 gram) with the average weight of the normal female adrenals (.6894 gram), it is apparent that there is a considerable difference in the two sexes; the normal male adrenal weights are approximately 20 per cent. greater than those of the normal females, the average of the body weights of the two sexes being almost identical.

Castration.—The average normal male adrenals (.8286 gram) compared with the average castrated male adrenal (.7538 gram) is 9.9 per cent. heavier. However, when average body weights are compared, one sees that the normal male is 7.6 per cent. heavier; the relative difference, therefore, is seen to be very small, though favoring slightly the normal animals. It appears, therefore, that castration inhibits the growth of the adrenals to a slight extent.

Spaying.—When the average weights of the normal female adrenals (.6894 gram) are compared with the average weights of

the spayed female adrenal (.5616 gram), one sees that the normal female adrenal is approximately 22.7 per cent. heavier than those of the spayed female. Since the body-weight comparison shows a difference of but 1 per cent., the conclusion is that spaying is followed by an inhibition of the growth of the adrenal gland.

Aside from the present data for the guinea pig there is apparently but one other set of data that gives an adequate comparison of the suprarenal weights in the two different sexes. Livingston's data ('16), consisting as it does of suprarenal weights at different ages and conditions of life, is inadequate for an intelligent comparison. Hatai ('15), however, found for the rat a marked sexual difference in the weights of the suprarenal glands. The female glands are approximately double those of the males in the mature animals. For the guinea pig there is also a decided sexual difference in the suprarenal weights, but in these animals it is the male that is the larger. At the end of one year the male suprarenals are approximately 20 per cent. greater in weight than those of the female.

Certainly to understand the general relationship existent between the suprarenals and the sex glands more data are desirable; particularly is this true for the guinea pig, in which the number of animals is inferior to that of the rat. Obviously it is useless to attempt an analysis of the conditions until the facts are well established.

One may well conclude that the same is true for the effects derived after gonadectomy, and particularly so in view of the many discrepancies noted in the literature. The fundamental conditions of the various experiments are so varied that only divergent results can be anticipated. Soli ('09) reports a decrease in the relative weight of the suprarenals after castration in guinea pigs, rabbits, and chicks, but the number of animals observed was small. Marrassini and Luciani ('11) reported considerable data on the suprarenal weights in both sexes of the rabbit and guinea pig after gonadectomy, but in their experiments the time limit was too brief for complete changes to have been registered. Castrated and spayed males and females were compared with normal animals of approximately the same age, but the operated animals were killed in all cases within ninety days after the operation, and sev-

eral were allowed to live but fifteen days after gonadectomy. The majority of the cases compared indicate a tendency toward a suprarenal hypertrophy in both sexes of the rabbit and guinea pig. Hatai ('15) found that the suprarenal of the male rat increased materially in weight after castration, whereas the female suprarenal showed a decrease of from 5 per cent. to 25 per cent. compared with normal females. In the guinea pig the relative weight of castrated and normal male suprarenals in my experiments are but little different. It appears, however, that there is a slight reduction in the weight of these glands in the castrated animals. In the spayed females the suprarenals were approximately 22 per cent. lighter in weight than those of the normal females.

The fundamental relationship between the sex glands and the suprarenals may be actually different for different types of animal forms, as is indicated by the discordant results reported. But it is undeniable that more exact data are necessary before an approach to the truth can be formulated. For the experimental data to be of value comparisons must be made with animals of similar ages and existing under similar living conditions. It is obvious, also, that data based upon considerable numbers of operated cases are of much greater weight than that obtained from a random comparison of a few animals.

VIII. Growth of the Spleen.

While the spleen is not ordinarily considered an organ of internal secretion, it appeared desirable to include the weights of this organ in the various animals, as all such data may prove of value at a later time.

Sexual Differences.—Comparing the average weight of the normal male spleen (1.0305 grams) with that of the average of the normal female spleen (1.0990 grams), one sees that the normal female spleen is 6.6 per cent. heavier than that of the male; since the average body weights are the same, we may conclude that there is a slight sexual difference in the spleen favoring that of the female.

Castration.—Comparing the average weight of the normal male spleen (1.0305 grams) with the average weight of the castrated male spleen (0.9037 gram), a slight difference is evident. The

normal male spleen is 14 per cent. heavier than the castrated male spleen, but the body weight of the normal male is 7.6 per cent. greater than that of the castrated male; the relative difference is therefore not so great. Apparently castration slightly inhibits growth of the spleen.

Spaying.—Comparing the normal female spleen with that of the spayed female spleen, we note that the spayed female possesses on the average a spleen 14 per cent. less in weight than the normal; since the body weights are but slightly different, we may conclude that spaying results in a decrease in the spleen growth.

IX. Bone Lengths.

Reported increases in the length of bones following gonadectomy indicate that the sex glands control to some degree the lengths acquired. In order to determine possible differences referable to a sex-gland disturbance, the bones of the hind leg of each animal of the series were measured at the time they were killed. These measurements are given in Table II. and are expressed in average lengths of the two similar bones from each animal. Thus the given femur length for each animal is the average between the lengths of the two femurs, etc., and it has been found that differences between the two bones are often greater than could be anticipated.

Sexual Differences.—When a comparison was made between average lengths of the hind-leg bones of the normal male group and an average of similar bones from the normal female group, it was found that the bones of the normal males were but slightly greater in length than those of the females. The difference was as follows: femur, 3.6 per cent. longer; tibia, 3.4 per cent. longer; fibula, 1.9 per cent. longer.

The sexual difference in bone lengths of normal guinea pigs is therefore one of slight degree, the males being favored as to growth in length.

Castration.—When the average lengths of the bones of the normal males were compared with similar ones of the castrated animals, the actual lengths were greater in the normal animals than in castrated ones; the femur was 2.5 per cent. greater in length, the tibia 1.7 per cent., and the fibula considerably less than 1 per

cent. greater in length than the corresponding bone of the castrated male. This actual difference, however, is minimized when it is remembered that the total body length of the normal males is approximately 6 per cent. greater than that of the castrated animal. If we compare the length of the bones as percentages of total body length, we find that each bone of the castrated animal is *relatively* longer than the corresponding bone of the normal animal (length of femur, as percentage of total body length, norm. 15.18 per cent., castrated 15.73 per cent.; tibia, norm. 16.44 per cent., cast. 17.18 per cent.; fibula, norm. 13.8 per cent., cast. 14.3 per cent. Since the relative lengths of the bones are greater in the castrated animals, the conclusion is that castration favors slightly growth in length of hind-leg bones. It must be emphasized, however, that this increase is not marked and careful computation must be employed to make it apparent. It appears so insignificant that little value is attached to it, and certainly the results are not in agreement with those who maintain that castration results in a marked overgrowth in bone lengths.

Spaying.—When the average bone length of the normal female group were compared with those of the spayed female group a decided difference in length was noted; the bone length of the spayed females was greater than similar bone lengths of the normal females. The observed length differences were as follows: femur, 2.4 per cent.; tibia, 3.6 per cent., and fibula 3.9 per cent. longer in spayed females than in normal females. When one considers that the total body length of the normal female was 2.4 per cent. greater than the spayed female, it is apparent that the *relative length* difference is greater than that of the *observed length.* We may conclude from this data that spaying in the guinea pig is conducive to greater lengths in hind-leg bones.

A number of investigators have reported exaggerated bone growth after gonadectomy, particularly in the absence of the testis. Poncet ('03), presenting a résumé of his own earlier experiments, as well as those of Pirsche ('02) and others, maintains that castration is followed by a general increase in the size of the skeleton. Observations on eunuchs, clinical cases of testicular atrophy, and experiments on laboratory animals were cited. In reference to the guinea-pig bones, he found an increase in length of 3 mm. for

the femur and 4 mm. for the tibia in castrated animals; the total lengths were not given, consequently the relative growths of bone in the two cases are unknown. In capons he found an increase of 8 mm. for the femur and 1 cm. for the tibia. Delay in the ossification of the epiphyses following castration is considered the causal factor for increase in length. Sellheim ('99) found delayed ossification in castrated vertebrates (pig, dog, and bull) and a consequent increase in size and length of bones. Hatai ('15) found a very slight increase in the ratio of body length to bone length in castrated rats. He mentions, however, that this difference appears only upon close computation, and is in doubt whether any significance should be attached to his findings.

X. Discussion.

The primary object in conducting the experiment reported herein was to study the reactions in weight of guinea pigs, from birth to maturity, as this may be influenced by the sex glands. Certainly secretions of the sex glands do modify somatic structures in many vertebrates and it has been assumed that weight of laboratory animals such as the rat and the guinea pig reflect, to some degree, their sexual nature; the differences are supposedly detectable if comparisons are made between the weights of normal animals and those having undergone operations at a previous date. However much one may be inclined to doubt the advocacy of utilizing weight as a criterion of sex-gland conditions, an intimate understanding of the reactions are necessary before the doubt can be expressed in definite form.

In the guinea pig (speaking of averages of groups of animals of the same age, same conditions as concerns sex glands, and reared under identical conditions) normal males are constantly heavier than normal females up to the end of the first year; at this time the weights between the two groups are almost identical and, according to Minot, the females subsequently become slightly heavier than the males. But does this mean that the testis promotes, and the ovary retards, growth and increase in weight? Elimination of the gonads of each sex should afford a basis for a partial answer to the question by comparing the growth curves of each group with that of the normal group. Referring to Fig. 1,

it is apparent that the gonadectomized groups fall below the curves of the normal groups for the greater part of the year; but by the 300th day the spayed females have attained the weight of the normal female and remain slightly above these until the close of the experiment. At the end of the experiment, therefore, the spayed females are heavier than normal females, whereas the castrated males are lighter in weight than the normal males. This appears to indicate that the testis does favor growth (absence reduces weight), and that the ovary retards growth (normal females lighter). But let us apply this evidence using as the basis of our comparison four females of the same litter, Y17, Y18, Y19, and Y20. These four sisters, reared together in the same cage, each show gradual growth throughout the year with an entire absence of temporary losses in weight; two had been spayed (Y17, Y18), while the other two remained normal females. On the 360th day each of the two spayed animals weighed 800 grams, one normal female (Y19) weighed 975 grams, and the other (Y20) weighed 745 grams. Since removal of the ovaries causes a relative increase in weight (when averages of entire groups were compared), the spayed females should weigh more than the normal ones. But referring to Table I., it becomes apparent that Y19 (normal) is 22 per cent. heavier than the spayed sisters, whereas Y20 is 2 per cent. lighter than the operated sisters. Our supposition, therefore, is proven that elimination of the ovary leads to relative increase in weight if the comparisons are made between these operated animals and Y20, but it is disproven if the comparisons are made with Y19 representing the normal condition. Consequently, if individual variations in weight are so great with animals of the same litter and lead to such discrepancies in results, one could not expect a more adequate basis of comparison if the animals of unknown history are chosen from the stock at random. One can not fail to be convinced of the magnitude of variation in weight in animals of the same age, sex, and under identical conditions if the weights on the 360th day are compared (Table I.); in some cases the individual variation is greater than 100 per cent. If, therefore, this group of total weights demonstrates nothing more (and indeed little is claimed for it), certainly it shows the fallacy of comparing at random the weights of two, three, or four

animals and claiming for it partial proof for an hypothesis. It appears that the claim of the writer is not only justified, but proven, that the weight of an animal as a character indicating the effect of a sex-gland graft is not only worthless as scientific data, but very confusing to the entire problem of the modifying effects of gonads.

In reference to the effects of gonadectomy on the weight of the glands of internal secretion, little will be added to the discussion in connection with each section of the paper. The great discrepancies in results, even diametrically opposed conclusions, of different investigators working with the same groups of animals have already been pointed out. The chief difficulties in adjusting the results from the various sources appear to center around inadequate controls for the experiments. Should one desire to study the effects of gonadectomy on such a structure as the hypophysis, it should be obvious that animals of similar strains, reared under similar conditions, operated at similar ages, and controlled by the proper groups are essential. Variations in general metabolism are not only so great among animals of different ages and strains that isolated comparisons often indicate inconsistent results, but even animals of the same litter may show marked differences.

The writer does not wish to imply that this experiment has been conducted in an ideal manner, but an attempt has been made to know, in so far as is possible, the history of the animal before and after operation, and to afford comparisons of groups of considerable size rather than mere isolated comparisons. Furthermore, it is realized that unknown conditions may have influenced the results herein reported and repetition is highly desirable before they can be accepted as of particular value.

As to the influence of gonadectomy on bone growth, the above criticisms apply as well. Growth in general body proportions is to a certain extent relatively constant for various parts. It should be supposed at once that a somewhat larger animal than a brother or sister would be expected, in general, to have longer bones and yet not show a specific reaction in bone growth conditioned by the presence or absence of sex-gland secretions.

The results of an analysis of the bone lengths of this group of

animals is surprising from the lack of more appreciable differences. In fact, the most clearly disproportionate length occurred in the spayed females. The bones of this group seem to reflect a specific effect of the absence of the ovarian secretion. The literature leads one to believe that differences between normal male and castrated male bone lengths is pronounced and easily detected. But the difference in lengths among the different groups of this experiment was so slight that careful computation was necessary to reveal it; the difference was so small that it appears almost insignificant.

Striking as may be the influence of the internal secretions of the sex glands on some characters in certain animal forms, it appears difficult and often impossible to discover characters in ordinary laboratory animals that are of sufficient difference and constancy in the two sexes to be capable of analysis by experimental procedure. And many of the characters cited in the literature supposedly offering a demonstration of the power of sexual secretions to effect modifications in the opposite sex fall to the ground if subjected to critical analysis. In the writer's opinion the character of weight reactions in guinea pigs belong to this group.

XI. Summary and Conclusions.

On the basis of observations on the guinea pig, herein reported, the following conclusions are drawn:

1. The curve of growth for normal male guinea pigs is consistently above that for normal females up to the end of the first year, when the two curves practically coincide.

2. Gonadectomy is followed by a decrease in the growth curves for both sexes; however, by the 300th day spayed females have reached the weight of normal females, and at the end of one year are 1 per cent. heavier than the normals.

3. The relative weight of a guinea pig is worthless as an indication of its sexual condition; properly controlled groups of weights may offer a debatable criterion of sex-gland effects, but random comparisons indicate nothing.

4. Total length of the animals correspond to total weights in the order: normal males > normal females > spayed females > castrated males.

5. The relative weight of the hypophysis of normal females is slightly greater than that of the normal males at the end of the first year.

6. Gonadectomy is followed by a relative reduction in weight of the hypophysis in operated males and females.

7. Thyroids of normal females are slightly heavier than those of normal males.

8. Gonadectomy appears to favor growth of the thyroids in both operated males and females.

9. Adrenals of normal male guinea pigs are approximately 20 per cent. greater in weight than those of normal females.

10. Gonadectomy is followed by a relative decrease in weight of adrenals in both sexes; though slight differences appear in males, the effect is considerably more pronounced in females.

11. The normal female spleen was found to be slightly heavier than that of the normal male.

12. Gonadectomy appears to cause a reduced growth of the spleen in both sexes.

13. The length of the hind-leg bones of the normal male is slightly greater than that of the normal female.

14. Castration favors, to a slight extent, the growth of leg bones in operated males, though the differences appear to be relatively insignificant.

15. Spaying is conducive to bone growth in operated females; the relative differences are considerably more pronounced than those following castration.

16. Repetition of the experiment is deemed highly advisable before the results, herein reported, are accepted as indicative of general principles.

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